Editorial Commentary

Towards understanding androgen receptor-independent prostate cancer: an evolving paradigm

Jianfu Zhou[1,2,3], Yuliang Wang[3], Songtao Xiang[1], Franky L. Chan[3]

[1]Department of Urology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510370, China; [2]The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou 510006, China; [3]School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

Correspondence to: Franky L. Chan. School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong, China. Email: franky-chan@cuhk.edu.hk.

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Prostate cancer (PC) arises as a distinctive androgen-driven malignancy, therefore androgen-deprivation therapy (ADT) targeting androgen receptor (AR) represents the mainstay treatment for conventional advanced adenocarcinoma. Although initially effective, a majority of tumors relapse with progression to a lethal castration-resistant prostate cancer (CRPC) (1). The latest use of next-generation AR signaling inhibitors (ARSIs), such as the steroidogenic enzyme CYP17A1 inhibitor abiraterone and antiandrogen enzalutamide, have resulted in life-extending benefits for the management of CRPC (2,3). However, a subset of highly aggressive transdifferentiated tumors emerges as AR-null/deficient/low heterogeneous phenotype with or without neuroendocrine prostate cancer (NEPC), which is characterized by the phenotypic shift of epithelial plasticity to a histologic subtype that morphologically resembles small-cell malignancy, resulting in eventual resistance to AR-directed therapies (4). The prognosis of these subtype of tumors is extremely poor and few treatment options exist.

The AR-independent plasticity is an emerging clinical entity in PC heterogeneity, especially in the next-generation AR antagonism era. In the era before the FDA approval of abiraterone and enzalutamide (1997–2011), most CRPCs presented AR-positive prostate cancer (ARPC; 85%) with few NEPCs (10%) and fewer AR-/NE- tumors (5%), thereby termed as "double-negative" PCs (DNPC). Whereas, in the current era with the clinical introduction of next-generation ARSIs (2012–2016), a shift of elevated AR-/NE- DNPC tumors (21%) and unaltered NEPCs (10%) were observed in a small minority of patients with both ARPC and NEPC tumors (5). A multi-institutional prospective study reported a 17% detection of overall incidence for treatment-emergent small-cell neuroendocrine prostate cancer (t-SCNC) of in a total of 202 mCRPC patients undergoing metastatic tumor biopsy. Most tumors (75%) showed upregulated nuclear AR protein expression and high serum PSA (>60 ng/mL), despite the classical features with AR-null phenotype and low serum PSA levels for *de novo* SCNC (6). Similarly, results from a recent study by Abida *et al*. showed that prostate tumors collected from 128 mCRPC patients treated with first-line next-generation ARSIs presented enriched histopathologic NE features (10.5%) after exposure to ARSIs as compared to ARSIs-naive tumors (2.3%) (7). These studies suggest that the heterogeneous process is an important mechanism responsible for the development of treatment-resistant mCRPC.

As to the underlying molecular determinants and mediators responsible for the heterogeneous setting, Liu and colleagues recently observed that a deficiency in AR abundance could lead to an increase of eIF4F-regulated translation initiation or protein synthesis in PTEN-deficient PC, which indicating a link between translational regulon and AR plasticity (8). Previous studies identified a few lineage plasticity-associated molecular events, for example genomic loss of the tumor suppressors *RB1* and *TP53* (9),

upregulation of lineage pluripotency transcription factors such as SOX2 (10), N-MYC (11) and ONECUT2 (12), epigenetic modifications including upregulation of EZH2 (13), elevation of FGF and MAPK kinase activities (5), dysregulation of Notch receptor pathway inhibitory ligand DLL3 (14), and overexpression of *TMPRSS2-ERG* fusion gene (15), etc. In addition, we also recently demonstrated that an orphan nuclear receptor TLX is capable of transcriptional repression of AR expression via an epigenetic mechanism, which contributes to AR plasticity and androgen insensitivity in CRPC (16).

Understanding the process and development of AR-independent PC can own certain translational relevance to clinical practice. Although the loss of AR expression eliminates the AR signaling as a therapeutic target, acquired treatment-emergent features of NEPC and other cancer stem-like cell phenotypes can exhibit novel targets and vulnerabilities. For instance, work led by Liu and colleagues revealed that PC patients presenting an upregulated translation initiation particularly with AR-low setting, may get benefit from the emerging eIF4F-targeted therapeutics. Indeed, the protein synthesis inhibitors are currently under investigation of phase-1 and -2 clinical trials (8). Other available drugs bypassing AR antagonism and designed with rationale of combination or co-targeting strategies, such as targeting AURK/RB1 axis, EZH2, DLL3, and FGF/MAPK, are also in development for AR-null/deficient/low or NEPC tumors (17).

In conclusion, lineage plasticity associated with loss of AR signaling dependence and the acquisition of NE features occurs in an approximately 15% of advanced PC patients. Understanding the district phenotypic shifts not only helps to gain insights into mechanisms underlying therapy-resistance but also provides novel strategies bypassing AR antagonism. Future studies are proposed to further outline the plasticity landscape in order to move forward our knowledge in treating transdifferentiated subtype tumors.

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Footnote

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